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Time Interval To Diagnosis Of Bladder Cancer And Its Associated Outcomes

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Lara K. Suh

2007

TIME INTERVAL TO DIAGNOSIS OF BLADDER CANCER AND ITS ASSOCIATED OUTCOMES. Lara K. Suh and Edward M. Uchio. Section of Urology, Department of Surgery, Yale University, School of Medicine, New Haven, CT.

The purpose of this study is to investigate whether a prolonged delay in diagnosis of bladder cancer will result in worse outcomes for those patients, compared to those patients with a shorter diagnostic time interval. Data was collected on 247 patients newly diagnosed with transitional cell carcinoma of the bladder from January 1996 to December 2006 (10 years). The medical records of these patients were reviewed for demographics, pathological stage, date of consultation to the genitourinary (GU) service, and date of diagnosis by transurethral resection of bladder tumor (TURBT). The specialty delay was calculated as the time between the date of consultation to the GU service to the establishment of a diagnosis by TURBT. Univariate analyses were performed to test the association of specialty delay with clinical features and all-cause mortality. The median specialty delay in this study was 100 days. There was a trend towards a longer specialty delay for muscle-invasive disease (T2-T4) in comparison to superficial disease (Ta and T1). There was a significant correlation between all-cause mortality and increasing clinical stage ($p=0.01$). There was a paradoxical finding that patients with a specialty delay greater than 100 days had a significant reduction in all-cause death in comparison to patients with a specialty delay of 100 days or less (relative risk=0.59; 95% CI 0.36-0.90; $p=0.01$). In conclusion, this study did not confirm the hypothesis that a prolonged specialty delay in patients diagnosed with bladder cancer would result in a worse prognosis. In fact, there was a paradoxical finding that patients with a specialty delay greater than the median delay of 100 days had a better prognosis.

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INTRODUCTION

Bladder cancer is the second most common malignancy of the genitourinary tract. In the United States, it is the fourth most common cancer in men, accounting for 6.2% of all cancer cases and it is the eighth most common cancer in women, accounting for 2.5% of all cancer cases (1). An estimated 61,420 individuals in the United States will be newly diagnosed with bladder cancer in 2006 (1). Of those individuals, 44,690 are male and 16,730 are female, making the incidence of bladder cancer more than 2.5 times more common in men (1). The estimated number of bladder cancer deaths expected to occur in the United States in 2006 is 13,060, of which 8,990 are male, making bladder cancer the ninth most common cause of cancer death in American men (1). Bladder cancer accounts for 3.1% of all cancer deaths in men and 1.5% in women. Up until the mid 1970s, the mortality rates for bladder cancer in the United States rose to a value of 5.1/100,000 in men and 1.5/100,000 in women, and then started to decline (2). The pattern of decline in mortality, which was observed mainly in men, reflects the pattern of decreased exposure to cigarette smoking and occupational carcinogens seen over the past two decades. These patterns are consistent with those of lung cancer mortality in men, which showed downward trends in countries that implemented antismoking campaigns.

Bladder cancer is primarily a disease of the elderly with the median age at diagnosis increasing from 69 years of age in the time period of 1974-1978 to 73 years of age in the time period of 1999-2003 (3). The incidence of bladder cancer also increases with age from roughly 142 per 100,000 men and 33 per

100,000 women age 65-69 years to 296 per 100,000 men and 74 per 100,000 women 85 years old or older (4).

Many different environmental exposures, which include occupational exposure to chemicals, cigarettes, caffeine, analgesics, drinking water quality, artificial sweeteners, and chemotherapeutic agents, have been studied in an attempt to determine a relationship with the development and progression of bladder cancer. However, only industrial chemicals and cigarette smoking have the epidemiologic, molecular, and histopathologic evidence to confirm this relationship. It has been estimated that between 4 and 7% of bladder cancer cases are attributable to occupational factors in Europe and up to 20% in the United States (2, 4). Most bladder carcinogens from occupational exposures are aromatic amines and their derivatives. Studies of German dye workers performed more than a century ago suggested that aniline containing dyes and arylamines, such as 2-naphthylamine, were responsible for the high incidence of bladder tumors seen in these workers (2). The association between bladder cancer and cigarette smoking is also well established. The relative risk (RR) that a smoker will develop bladder cancer is 2-4 times that of non-smokers (2). This risk increases with the number of cigarettes smoked, the duration of smoking, and the degree of inhalation of smoke (4). There is also an association with smoking cessation and a decline in the relative risk of bladder cancer that is proportional to the duration of abstinence (2). Although epidemiologic and experimental evidence favors a strong role for chemical carcinogens in the

etiology of bladder cancer, many cases arise with no obvious exposure to known carcinogens.

The spectrum of bladder cancer includes superficial, muscle-invasive, and metastatic disease, each with its own clinical behavior, prognosis, and treatment. Approximately 90% of all bladder cancers are transitional cell carcinomas, and all further discussion of bladder cancer in this study will refer to transitional cell carcinoma. The most commonly used staging system is the American Joint Committee on Cancer TNM system, which allows for a precise and simultaneous description of the primary tumor stage, the status of lymph nodes, and metastatic sites. Papillary bladder tumors that are limited to the bladder epithelium are classified as stage Ta lesions, while any tumor invading the lamina propria or submucosa is classified as a stage T1 tumor. Any lesion that invades into the muscle, but is still confined within the bladder is classified as a stage T2 tumor. The T3 category includes tumors that invade the perivesical fat and T4 disease includes tumors that extend into adjacent organs. Carcinoma in-situ (CIS) is a flat lesion of the urothelium characterized by the presence of cells containing large, irregular hyperchromatic nuclei with prominent nucleoli. CIS disease has a variable natural history, but many cases progress to invasive disease. At the time of diagnosis, approximately 70% of bladder tumors are classified as superficial disease (stage Ta, T1, and CIS) and the remaining 30% are muscle-invasive bladder tumors (stage T2 to T4) (5). Among the superficial bladder tumors, 70% present as Ta lesions, 20% as T1 lesions, and 10% as carcinoma in-situ (5). The clinical stage of a bladder tumor provides a reasonable estimate

of its biologic potential and it is strongly correlated to tumor recurrence, progression, and survival. For those patients with disease limited to the submucosal layer and above, which includes stage Ta, T1, and CIS, the disease-free survival is 80-88%. For patients with muscle-invasive bladder cancer, the disease-free survival steadily declines: 53-80% for T2, 39-68% for T3, and 25-40% for T4 tumors (6).

Bladder tumors are also classified by histologic grade as either low or high grade, based upon the degree of resemblance to the normal tissue architecture. About 60% of newly diagnosed bladder tumors are low-grade, superficial (stage Ta or T1) lesions. The remaining 40% of newly diagnosed bladder tumors are high-grade lesions, with more than half of those being muscle-invasive (stage T2 or above) at the time of diagnosis (7). The most important prognostic parameters for tumor recurrence and subsequent cancer progression are tumor grade, tumor stage, and presence of carcinoma in-situ.

Superficial bladder cancer includes those stages that are not muscle-invasive, stages Ta, T1, and CIS, and represents a spectrum of tumors with a wide range of clinical behaviors. Multiple recurrent low-grade Ta tumors have a high risk of recurrence but a low risk of progression into muscle-invasive disease. On the other hand, multiple recurrent high-grade T1 tumors have a high risk for both recurrence and progression. For those patients diagnosed with superficial bladder cancer, the most important prognostic factors for recurrence are the number of tumors, their size, and the prior recurrence rate (8). A multivariate analysis of prognostic factors performed by Millan-Rodriguez et al. (9)

demonstrated that the only mortality prognostic factors are high-grade disease and carcinoma in-situ. They found that high grade disease has a 14 times higher mortality risk than that of low grade disease (95% CI 1.8-109) and associated carcinoma in-situ had a 3 times higher mortality risk than without CIS disease (95% CI 1.4-6.6). A study of 333 patients with superficial bladder cancer by Allard et al. (10) demonstrated that the probability of recurrence at one year after transurethral resection (TURBT) increased with the presence of certain tumor characteristics: multiplicity, tumor size > 3cm, stage T1, and high grade. A patient with superficial bladder cancer and none of the aforementioned tumor characteristics has about a 15% probability of recurrence at one year, while a patient with 3 or 4 of the tumor characteristics will have a 70% probability of recurrence at one year. Kurth et al. (11) studied 576 patients with superficial bladder tumors and found that tumors recurred in 54% of the study group and 76 patients progressed to T2 or worse. The study also observed a tumor progression rate ranging from about 7% to 41%, depending on three main factors: tumor size, grade, and prior recurrence rate.

The clinical stage and grade of a bladder tumor is also an important variable in tailoring treatment decisions for patients diagnosed with bladder cancer. Patients with low grade, small Ta tumors who are at low risk of progression may be treated with transurethral resection alone, followed by surveillance. Patients with high grade, large T1 tumors who are at a higher risk of progression and recurrence are candidates for intravesical chemotherapy following complete transurethral resection or early cystectomy, especially if the

presentation is multifocal. For patients with muscle-invasive bladder cancer, the treatment of choice is radical cystectomy. Improvements in surgical technique and perioperative care have reduced perioperative mortality to 3% and overall survival after radical cystectomy is 60% at 5 years (12). Recent studies have suggested that a delay in radical cystectomy for the treatment of muscle-invasive bladder cancer can adversely affect patient survival and result in worse pathological stage. Sanchez-Ortiz et al. (13) studied 290 patients who underwent radical cystectomy for muscle-invasive bladder cancer and found that a delay in surgery of greater than 12 weeks was associated with advanced pathological stage and decreased survival. Chang et al. (14) studied 303 patients with muscle-invasive bladder cancer who underwent radical cystectomy to determine whether a delay in treatment influenced pathological staging outcome. This study found that 81% of the patients with a treatment delay of greater than 90 days had stage T3 or higher disease, compared to 52% of those patients with a treatment delay less than 90 days (81% versus 52%, chi-square analysis $p=0.01$). Lee et al. (15) studied the timing from stage T2 bladder cancer diagnosis to radical cystectomy and its impact on survival. This study observed a significant disease specific survival and overall survival advantage in patients treated 93 days or less compared to greater than 93 days ($p=0.05$ and 0.02 , respectively).

Similar studies have been performed to evaluate the impact of treatment delays for prostate cancer. The SEARCH database study group (16) studied almost 900 men with low risk prostate cancer who underwent radical

prostatectomy and observed an increased risk of biochemical progression in men with delays of greater than 180 days compared to a delay of less than 90 days (RR 2.75, 95% CI 1.40 to 5.43). Similarly, Nguyen et al. (17) found that delays in initiating radiation therapy adversely influence PSA outcome in patients with high-risk disease. In their cohort of high-risk patients, the PSA failure-free survival estimates at 5 years for patients with a delay less than 2.5 months was 55%, compared to 39% for patients with a delay of 2.5 months or more ($p=0.014$).

These studies investigated only the treatment delay, defined as the time interval from diagnosis to treatment. However, delayed treatment for a disease is comprised of two components, the diagnostic delay and the treatment delay. The diagnostic delay can be further divided into the patient delay and the hospital delay (see Figure 1). The patient delay is defined as the time interval from the patient's first awareness of symptoms to the first medical consultation. The hospital delay is defined as the time interval from the medical consultation to the diagnosis. At healthcare providers, such as the Veterans Affairs (VA) Connecticut Healthcare System, the hospital delay can be further divided into two phases, the primary care delay and the specialist delay. The primary care delay is defined as the time interval from consultation with a primary care physician (PCP) to the first specialty consultation. The specialty delay is defined as the time interval from the first specialty consultation to diagnosis.

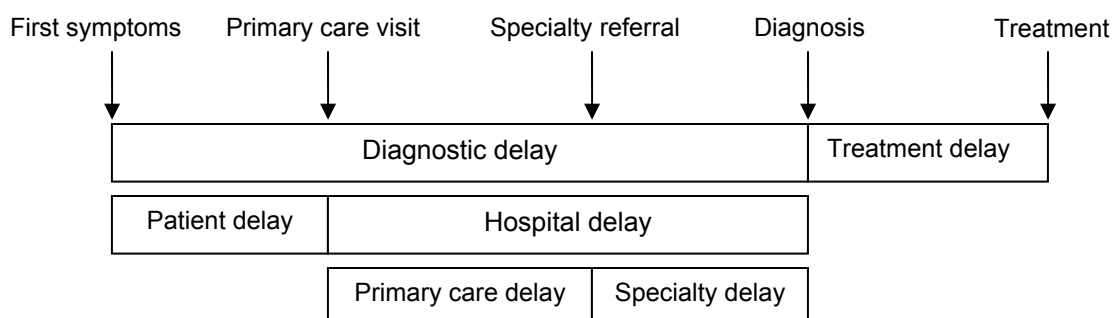


Figure 1. The different components of delay from first symptom to treatment.

Although, there have been recent studies investigating the consequences of a prolonged treatment delay in bladder cancer, there have been few studies evaluating the effect of a prolonged diagnosis delay in the outcomes of bladder cancer patients. The assessment of diagnostic delay is difficult to study because of the variations in referral methods, which can differ according to the patient's insurance coverage and whether their physician is in a private practice setting or in an academic setting. A study to assess diagnostic delay is best performed within a healthcare system that includes primary care physicians and a standardized referral method, such as a Health Maintenance Organization (HMO) or a Veterans Administration (VA) system. One such study of diagnostic delay by Liedberg et al. (18) found that patients with T1 bladder tumors and a diagnostic delay of greater than 6 months showed a relative risk of bladder cancer death of 2.0 (95% CI 0.84-4.7; $p=0.12$), compared to those with a shorter delay. However, patients with muscle invasive tumors (stage T2-T4) with a greater than 6 month diagnostic delay had a relative risk of bladder cancer death of 0.39 (95% CI 0.23-0.69; $p=0.001$). There has been mixed evidence regarding

the affects of a delayed diagnosis on survival and prognosis for other malignancies, such as breast cancer, colorectal cancer, and lung cancer (19-21).

Mansson et al. (22) investigated the various factors that may play a role in the different components of delay in the diagnosis of bladder cancer. They found that the median patient delay was 15 days (mean 141, range 0-2857) and there was no relationship between this delay and age or gender. However, they did find that the type of symptoms was an important factor in patient delay with hematuria prompting patients to seek medical advice more quickly than urgency of micturition or pain (median 5 days vs. 45 and 38 days, respectively, $p < 0.001$). The median hospital delay was 62 days overall with a positive correlation between hospital delay and the number of referrals. As with patient delay, the type of presenting symptoms influenced hospital delay: hematuria with pain had a shorter delay than hematuria alone, and urgency had the longest delay (medians 44, 53 and 114 days, respectively, $p < 0.001$). When comparing tumor stage in relation to delays, the median patient delay was longer with advanced cancer than in those with superficial tumors, but this difference was not statistically significant. No correlation was found between tumor stage and hospital delay.

The results of these studies demonstrate that the impact of a prolonged diagnostic and/or treatment delay on prognosis is complex and a better understanding of this relationship is needed.

HYPOTHESIS

This study will test the hypothesis that a prolonged delay in diagnosis of transitional cell carcinoma of the bladder will result in worse outcomes for those patients compared to those patients with a shorter diagnostic time interval.

SPECIFIC AIMS

The primary aim of this study is to investigate the diagnostic delay for patients newly diagnosed with bladder cancer at the VA Connecticut Healthcare Systems and its association, if any, to bladder cancer recurrence and all-cause mortality.

This primary aim will be achieved by the following:

1. Calculation of the specialty delay, defined as the time interval from genitourinary (GU) service consultation to diagnosis of bladder cancer, for all study subjects.
2. Determine if there is an association between a prolonged specialty delay (greater than 100 days) and incidence of bladder cancer recurrence.
3. Determine if there is a relationship between a prolonged specialty delay (greater than 100 days) and incidence of all-cause death.

A secondary aim of this study is to determine the clinical outcomes of patients newly diagnosed with bladder cancer at the VA Connecticut Healthcare Systems.

This secondary aim will be achieved by the following:

1. Determine the distribution of clinical stages in patients newly diagnosed with bladder cancer at the VA Connecticut Healthcare Systems.

2. Determine the mean specialty delay for the entire study cohort and for each clinical stage.
3. Determine if there is a relationship between specialty delays and clinical stage.
4. Determine the incidence of bladder cancer recurrence and all-cause death for the entire study cohort and for each clinical stage.
5. Determine if there is a relationship between clinical stage and incidence of all-cause death.

METHODS

Data on patients diagnosed with bladder cancer from 1996 to 2006 (10 years) were reviewed after obtaining Institutional Review Board approval from the Veterans Affairs Connecticut Healthcare Systems. The analyzed data derived from 317 subjects with the diagnosis of malignant neoplasm of the bladder made at the VA Connecticut Healthcare Systems. A report was generated by the Department of Surgery at the VA Connecticut Healthcare Systems using the International Classification of Disease (ICD-9 billing codes 188.0 through 188.9), which identified all patients diagnosed with a malignant neoplasm of the bladder from January 1996 to December 2006. Of the 317 cases, 42 subjects were excluded because there were no referrals to the genitourinary (GU) service noted in their medical records, so a specialty delay interval could not be calculated. An additional 28 patients were excluded from

the study for recurrent bladder cancer (n=19), squamous cell carcinoma (n=4), adenocarcinoma (n=3), sarcomatoid carcinoma (n=1), and small cell carcinoma (n=1). The remaining 247 patients with a diagnosis of transitional cell carcinoma of the bladder established in January 1996 through December 2006 comprised the study cohort.

The data collected included the date of consultation to the GU service, the date of diagnosis, and the dates of any recurrences diagnosed by transurethral resection of bladder tumor (TURBT). Patients were referred to the GU service by their primary care physician using the electronic consult request in the patient's electronic medical record. In most instances, the date of referral to the GU service corresponds to the date the patient first presents to their primary care physician with their urinary symptoms (i.e. gross hematuria, dysuria, urgency of micturition, etc.). The date of diagnosis is defined as the date of the patient's TURBT that initially revealed a malignancy of the bladder on pathology report. Pathology reports for all follow-up TURBT's were reviewed for evidence of recurrent malignant bladder tumors. Information on the patient's status at the time of censor (February 1, 2007) was also collected. The date of the patient's last follow-up visit, if alive, or the date of death was noted. Clinical details collected included the number and size of tumors. Pathological details and American Joint Committee on Cancer (AJCC) TNM classification were also collected. Information on demographics, such as age and gender, were also collected.

Following the collection of the data, all identifying information (name, patient ID number, SSN) was removed from the data set and was filed separately, with access limited to responsible investigators. All records reviewed remained confidential and any analytical use of the records did not refer to identifying information.

For those patients who were alive at the censor date, the follow-up interval was calculated as the time from diagnosis to the latest date of bladder cancer recurrence, or the censor date for patients who did not experience a recurrence. For those patients who did not survive during the study period, the follow-up interval was calculated as the time from diagnosis to the date of death. The mean follow-up interval was calculated for the entire cohort.

The specialty delay interval was calculated as the time from consultation to the GU service to the diagnosis by TURBT. The mean specialty delay was calculated for the entire cohort and for each clinical stage. The mean specialty delay was also calculated for those patients diagnosed with superficial disease, defined as clinical stage Ta and T1, and muscle-invasive disease, defined as clinical stage T2 through T4. A one-way analysis of variance (ANOVA) was used to compare the mean specialty delays between each of the clinical stages using the Statistical Analysis ToolPak (Microsoft Excel, Microsoft Corp., Redmond, WA). An unpaired Student's t-test was used to compare the mean specialty delays of the superficial disease group and the muscle-invasive disease group.

The number of patients with a recurrence of malignant bladder tumor diagnosed on a follow-up TURBT was used to calculate the incidence of

recurrence. Following stratification by clinical stage, the incidence of recurrence was only calculated for stage Ta and T1. The incidence of recurrence was not calculated for the muscle-invasive tumors (clinical stage T2 through T4) since the standard of treatment for these patients would be a radical cystectomy and recurrence in the bladder would not occur.

The number of patients who died from any cause was used to calculate the incidence of all-cause death for each clinical stage. A regression analysis was performed to determine the relationship between all-cause death and increasing clinical stage using the Statistical Analysis ToolPak in Microsoft Excel.

The entire cohort was divided into two specialty delay groups using the median specialty delay of 100 days, which led to one specialty delay group of 100 days or less and another specialty delay group of greater than 100 days. For patients diagnosed in each superficial clinical stage, the incidence of bladder tumor recurrence was calculated for both of the specialty delay groups. Relative risk ratios were calculated comparing those patients with a specialty delay of greater than 100 days versus those patients with a specialty delay of 100 days or less. Two-group comparisons were performed using the Fischer's exact test (GraphPad Software, San Diego, CA). For the entire cohort, the incidence of death from all causes was calculated for both specialty delay groups. The incidence of disease-specific death was not calculated in this study due to unavailability of data regarding cause of death. Relative risk ratios were calculated and two-group comparisons were performed using the Fischer's exact

test, as described above. All relative risk ratios were calculated with 95% confidence intervals and all P-values were two-sided.

RESULTS

Overall, 247 patients met the criteria for inclusion in this study.

Demographic and pathologic features of the patients from the overall cohort are shown in Table A. The cohort consisted of 244 men (98.8%) and 3 women (1.2%) with a mean age of 70.5 years (standard deviation 9.8) and a mean follow-up interval of 2.8 years (range 12 days to 11.1 years). The majority of the cohort had superficial bladder cancer at the time of diagnosis, with 120 patients presenting with clinical Ta disease and 81 patients with clinical T1 disease. Six patients had only carcinoma in-situ (CIS) disease at diagnosis, while the remaining 40 patients had muscle-invasive bladder cancer (34 patients with T2 disease, 3 patients with T3 disease, and 3 patients with T4 disease).

Table A. Demographic characteristics

	No. Pts. (%)
Study cohort	247 (100)
Mean age \pm SD	70.5 \pm 9.8
Males	244 (98.8)
Females	3 (1.2)
Clinical stage:	
CIS	6 (2.4)
Ta	120 (48.6)
T1	81 (32.8)
T2	34 (13.8)
T3	3 (1.2)
T4	3 (1.2)

The mean time interval from referral to the GU service to the diagnosis of bladder cancer by TURBT (specialty delay) for the entire cohort was 179 days (6.0 months). The specialty delay for the entire cohort ranged from 0 to 1,417 days, with a median of 100 days. Table B summarizes the specialty delay for all patients stratified by clinical stage. A one-way ANOVA demonstrated that there was no statistical difference of the mean specialty delays between the clinical stages ($p=0.96$).

Table B. Specialty delays stratified by clinical stage. SEM=standard error of measurement.

Clinical Stage	No. Pts.	Mean Specialty Delay (days)	Range (days)	SEM (days)
Ta	120	184	2-1288	20.2
T1	81	166	0-1417	27.4
T2	34	194	2-1086	48.1
T3	3	180	41-280	71.7
T4	3	233	24-647	207.0
CIS	6	151	29-465	66.8

The mean specialty delay for those patients with superficial disease, defined as stage Ta and T1, was 176 days with a standard error of measurement (SEM) of 12.0. The mean specialty delay for those patients with muscle-invasive disease, defined as stage T2, T3, or T4, was 228 days (SEM 28.4). Figure 1 demonstrates that the patients presenting with muscle-invasive bladder cancer have no statistically significant difference in specialty delay, in comparison to those patients with superficial disease (Student's t-test, two-tail $p=0.10$).

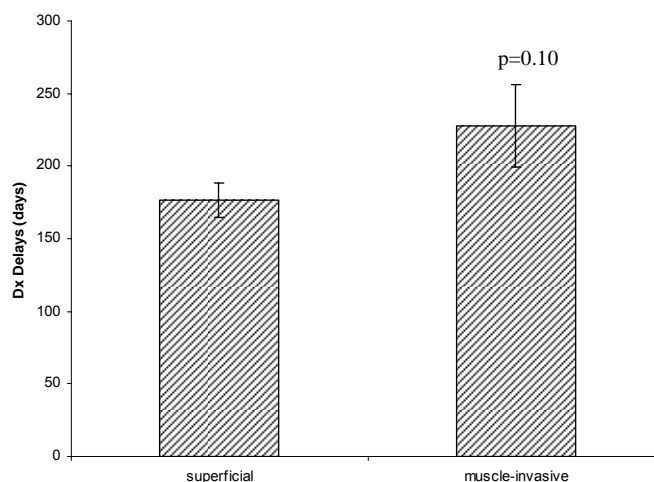


Figure 1. Mean specialty delays for superficial disease (n=202) and muscle-invasive disease (n=41) [Student's t-test, $p=0.10$].

Table C summarizes the incidence of bladder cancer recurrence on follow-up TURBT for those patients who were initially diagnosed with clinical stage Ta, T1, or CIS bladder cancer. Bladder cancer recurrence was not chosen as an endpoint for patients with muscle-invasive disease (T2-T4) since treatment with radical cystectomy is the standard of care. The incidence of bladder cancer recurrence was similar for patients with stage Ta, T1, and CIS disease. Table C also summarizes the incidence of all cause death for the cohort stratified by clinical stage. The patients with muscle-invasive bladder cancer (T2-T4) have a two-fold increase in all-cause death, compared to the patients who present with superficial bladder cancer (50.0% versus 25.4%, respectively, $p=0.004$). Patients with stage Ta disease had the lowest incidence of all-cause death at 24.2% and patients with stage T4 disease had the highest incidence of all cause death. On regression analysis, there was a statistically significant correlation between

increasing clinical stage and an increased incidence of all cause death ($p=0.01$, see Figure 2).

Table C. Bladder cancer recurrence and death by any cause stratified by clinical stage.

Clinical Stage	No. of Pts with Recurrence (%)	No. of Pts with All-Cause Death (%)
Ta (n=120)	55 (45.8)	29 (24.2)
T1 (n=81)	35 (43.2)	22 (27.2)
T2 (n=34)	--	15 (44.1)
T3 (n=3)	--	2 (66.7)
T4 (n=3)	--	3 (100)
Superficial (n=201)	90 (44.8)	51 (25.4)
Muscle-Invasive (n=40)	--	20 (50.0)

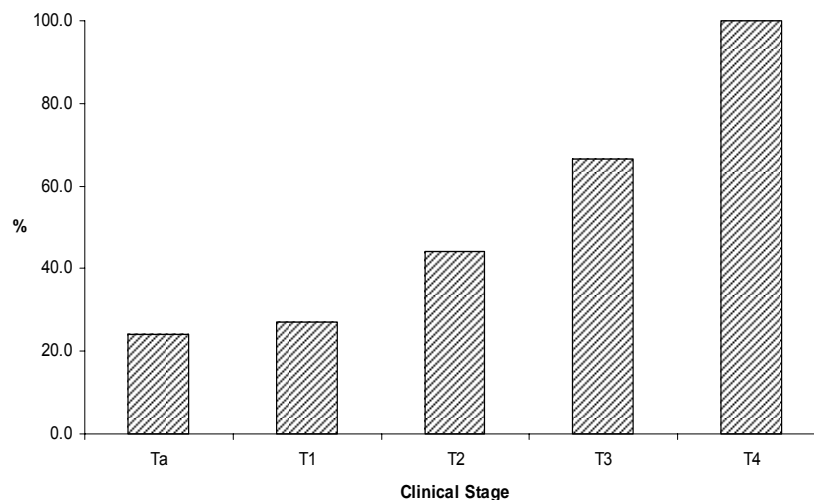


Figure 2. Incidence of death by any cause, demonstrating an increased incidence of death with increased clinical stage (regression analysis, $p=0.01$).

Figure 3 demonstrates a reduced incidence of bladder cancer recurrence in those patients with a specialty delay of greater than 100 days compared to

those patients with a diagnosis made 100 days or less, however the reduction was not statistically significant for all groups. For those patients with superficial disease (Ta and T1; n=201) and a specialty delay of greater than 100 days, there was a trend towards a reduction in bladder cancer recurrence compared to those patients with a specialty delay of 100 days or less (Relative Risk=0.78; 95% CI 0.57-1.06; p=0.12). Table D summarizes the relative risk of bladder cancer recurrence for patients with a specialty delay of 100 days or less compared to those with a specialty delay of greater than 100 days.

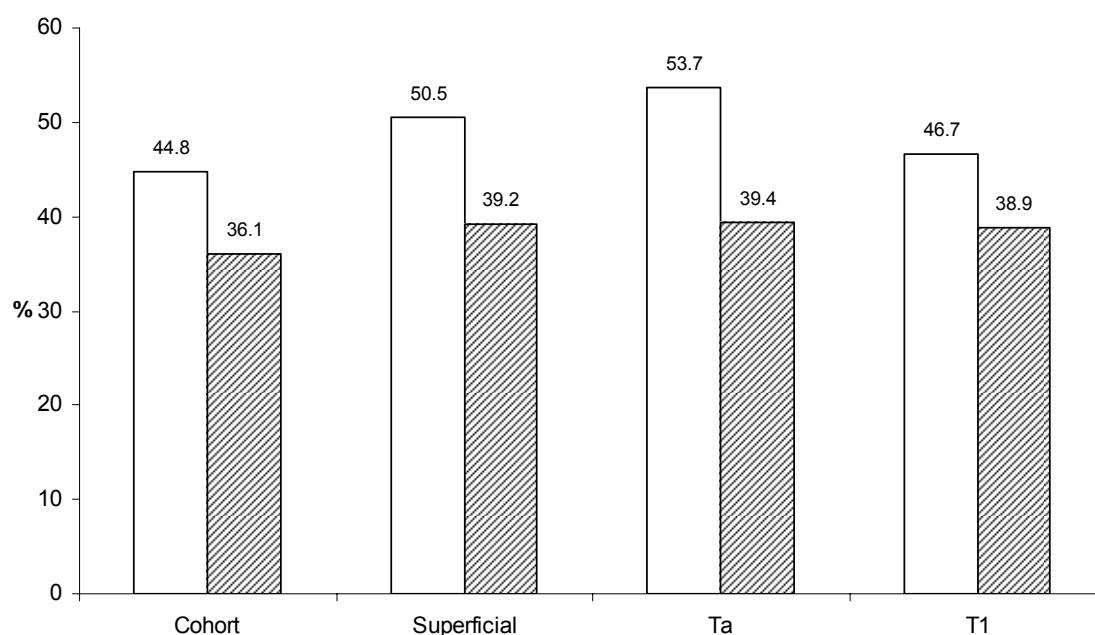


Figure 3. Bladder tumor recurrence in patients with a specialty delay of 100 days or less (open boxes) compared to greater than 100 days (hatched boxes), stratified by clinical stage.

Table D. Relative risk of bladder cancer recurrence for specialist delay >100 days compared to ≤100 days.

Specialist delay >100 days	Relative Risk	95% CI	p-Value
Entire Cohort	0.81	0.59-1.09	0.19
Superficial Disease (Ta and T1)	0.78	0.57-1.06	0.12
Clinical Stage Ta	0.73	0.50-1.08	0.14
Clinical Stage T1	0.83	0.57-1.49	0.51

Figure 4 demonstrates a reduced incidence of all-cause death in those patients with a specialty delay of greater than 100 days when compared to those patients with a specialty delay of 100 days or less. For the entire cohort, patients with a specialty delay of greater than 100 days had a decreased risk of death compared to those with a specialty delay of 100 days or less (RR=0.59, 95% CI 0.36-0.90; p=0.01). For patients diagnosed with muscle-invasive bladder cancer, there was no statistical difference in the incidence of all-cause death between those patients diagnosed 100 days or less and those with a specialty delay of greater than 100 days (see Table E). However, for patients diagnosed with superficial bladder cancer, there was a statistically significant reduction in the incidence of all-cause death for those patients with a specialty delay of greater than 100 days compared to those with a shorter specialty delay (RR=0.53, 95% CI 0.32-0.88; p=0.01). Patients with stage Ta disease also had a statistically significant reduction in the incidence of all cause death (RR=0.50, 95% CI 0.26-0.97; p=0.05).

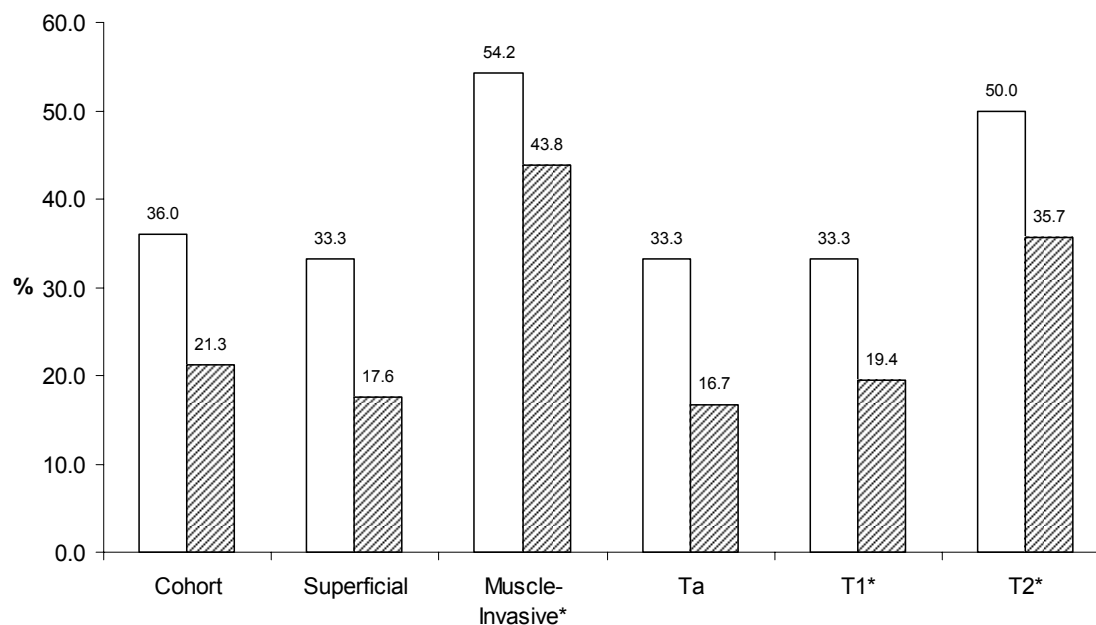


Figure 4. All-cause mortality rate in patients with a specialty delay of 100 days or less (open boxes) compared to greater than 100 days (hatched boxes).

*not statistically significant ($p > 0.05$)

Table E. Relative risk of death from all causes for specialist delay >100 days compared to ≤100 days.

Specialist delay >100 days	Relative Risk	95% CI	p-Value
Entire Cohort	0.59	0.36-0.90	0.01
Superficial Disease (Ta and T1)	0.53	0.32-0.88	0.01
Muscle-Invasive Disease (T2-T4)	0.81	0.41-1.57	0.75
Clinical Stage Ta	0.50	0.26-0.97	0.05
Clinical Stage T1	0.58	0.27-1.28	0.21
Clinical Stage T2	0.71	0.31-1.64	0.50

DISCUSSION

It is difficult to compare the median specialty delay of 100 days found in this study to delays found in other studies because of the various different definitions of diagnostic delays. Wallace et al. (23) have the most similar definition, with a specialist delay defined as the date of general practitioner (GP) referral to the date of first treatment by transurethral resection of bladder tumor (TURBT). They reported a median specialist delay of 68 days (range 34-118 days), which is over one month shorter than the median delay observed in this study at the VA Connecticut Healthcare System. Liedberg et al. (18) defined a diagnostic delay as the time lag from the patient's first awareness of symptoms to the establishment of a correct diagnosis, and observed a median diagnostic delay of 144 days. This diagnostic delay definition includes the patient delay, defined as the time lag from the patient's first awareness of symptoms to the first medical consultation, and the hospital delay, defined as the time lag from that consultation to the establishment of a diagnosis. Unfortunately, a direct comparison to this study cannot be made since they did not report the specialist delay separately from the diagnostic delay. Mansson et al. (22) studied the hospital delay in 343 patients diagnosed with bladder cancer and observed a median hospital delay of 62 days. The hospital delay of 62 days observed by Mansson et al. (22) is considerably shorter than the median specialty delay of 100 days observed in this study, especially given the fact that the hospital delay includes the delay from first medical consultation to specialist consultation.

When the specialty delay was stratified by clinical stages, there was no difference observed in the mean delays. This observation could be the result of low sample sizes in each clinical stage, especially for stage T3 and T4, which had three patients in each group. The low sample size in these two groups led to high standard errors of the mean, which contributes to the statistical analysis. However, when the clinical stages were grouped into superficial disease (stage Ta and T1) and muscle-invasive disease (stage T2-T4), there was a more pronounced difference in the mean specialty delays. The muscle-invasive group had a mean specialty delay that was 52 days longer than the superficial group (228 days versus 176 days; $p=0.10$). Although the difference was not statistically significant, a trend was seen towards a longer specialty delay with more advanced clinical stage. This result is consistent with observations made in the Swedish study by Liedberg et al. (18). They observed a median diagnostic delay of 124 days and 157 days in the T1 and T2-T4 tumor groups, respectively. When they compared the diagnostic delays for each tumor stage, there was a significantly longer diagnostic delay in patients presenting with more advanced tumor stages (test for trend, $p=0.02$).

Our study observed a statistically significant increased incidence of all-cause mortality with more advanced tumor stage ($p=0.01$). Recent studies have found a similar relationship between advanced tumor stage and mortality. Wallace et al. (23) observed a significant association between death and tumor stage, indicating that patients with T2-T4 tumors were more likely to die from bladder cancer than patients with Ta and T1 tumors (test for trend, $p<0.001$).

Similarly, Liedberg et al. (18) found that tumor stage strongly correlated ($p < 0.001$) with cumulative incidence of bladder cancer death.

The hypothesis for our study was that a prolonged specialty delay in patients newly diagnosed with bladder cancer would result in a worse prognosis compared to those patients with a shorter delay. However, the results of this study did not confirm this hypothesis. In fact, there was a paradoxical finding that patients with a specialty delay greater than the median delay of 100 days had a better prognosis. Patients who were newly diagnosed with bladder cancer within 100 days from the consultation to the GU service had a higher all-cause mortality rate than those patients diagnosed after 100 days (36% versus 21.3%, respectively). The reduction in the all-cause mortality rate was statistically significant in those patients with a specialty delay greater than 100 days, compared to those with a delay of 100 days or less ($RR = 0.59$; 95% CI 0.36-0.90; $p = 0.01$). In a U.K. study by Wallace et al. (23) a similar relationship was observed between hospital delay and survival. They studied 1,537 patients and compared overall survival between those patients with a hospital delay of 68 days or less and those patients with a hospital delay of greater than 68 days. They observed that the patients with a shorter hospital delay (68 days or less) had a significantly worse overall survival in comparison to the patients with a prolonged hospital delay ($p = 0.001$). Even after adjusting for tumor stage, the worse overall survival seen in the shorter hospital delay group continued to be statistically significant ($p = 0.01$).

When the patients with superficial disease (stage Ta and T1) in our study were analyzed separately, a statistically significant reduction in all-cause mortality continued to be observed in the group with a specialty delay of more than 100 days (RR=0.53; 95% CI 0.32-0.88; $p=0.01$). Although the patients with muscle-invasive disease (stage T2-T4) who had a specialty delay of more than 100 days had a lower all-cause mortality rate compared to those diagnosed within 100 days, it was not statistically significant ($p=0.75$). These findings are not consistent with those observed in a Swedish study by Liedberg et al. (18) who studied the affects of diagnostic delays on bladder cancer death in 177 patients with bladder cancer. They found that among patients with T1 tumors, those with a diagnostic delay of more than 6 months showed a trend, although not statistically significant, towards an increased risk of bladder cancer death (RR=2.0; 95% CI 0.84-4.7; $p=0.12$). They also observed that in the group with muscle-invasive tumors (T2-T4) who had a diagnostic delay of more than 6 months, had a statistically significant reduction in bladder cancer death (RR=0.39; 95% CI 0.23-0.69; $p=0.001$). A possible contributing factor to the significant result Liedberg et al. (18) were able to observe in the muscle-invasive group, compared to the observation seen in our study could be due to the difference in sample size. The Swedish study had 103 patients in the muscle-invasive group, compared to 40 patients in our study.

The findings of our study initially seem counter-intuitive, but biased patient selection could explain why an increased specialty delay is associated with improved prognosis. Those patients who were found to have large, solid-looking

tumors at flexible cystoscopy in the office may have been prioritized for early transurethral resection and conversely, patients found to have small, papillary tumors at flexible cystoscopy may have been considered as requiring transurethral resection less urgently. This triage effect is predominantly seen in hospital settings with limited resources, resulting in longer wait times for operating room scheduling and physician availability to perform transurethral resection of the bladder tumor (TURBT). Thus, patients with rapidly progressing tumors with a poor prognosis might have undergone early TURBT and diagnosis after visualization of the tumor by flexible cystoscopy and triaging by the specialist in the outpatient setting. To study diagnostic delay without the triage effect would require a hospital setting with an excess of resources available to eliminate the scheduling delays for TURBT. In this scenario, every patient would have access to timely TURBT regardless of the appearance of the patient's bladder tumor on flexible cystoscopy.

The patient's presenting symptoms, such as gross hematuria versus microhematuria, may have also altered decisions about the priority of transurethral resection. Mansson et al. (22) studied delays in diagnosis, and found that the hospital delay (time interval from first medical consultation to the establishment of a correct diagnosis) was strongly influenced by the presenting symptoms of the patient. The median hospital delay for patients presenting with hematuria plus pain was 44 days, for hematuria alone was 53 days, and for urgency of micturition alone was 114 days ($p < 0.001$). The severity of signs and symptoms at presentation may perhaps influence the speed of the medical

decision process and give patients with severe disease priority for diagnosis and treatment, which could correlate with worse prognosis.

Studies of diagnostic delays in other malignancies have also demonstrated an improved survival in patients with longer delays (20, 21, 24). Rupassara et al. (20) studied 154 patients diagnosed with colorectal cancer and divided the study group into a Late group and an Early group. The Late group was defined as patients who had to wait more than or equal to 50 days from the date of receipt of a referral letter to the date of diagnosis. The Early group was comprised of patients who had a referral to diagnosis time less than 50 days. They found that the Late group had a 93.7% cancer-specific five year survival, compared with 65.3% in the Early group ($p=0.007$). Similar findings have been observed in studies of patients diagnosed with lung cancer. Salomaa et al. (21) studied 132 patients diagnosed with lung cancer and measured different delays from first symptoms to treatment. They looked at the specialist treatment delay (delay time between the first visit to the specialist and the date of the beginning of treatment) in relation to survival. They found that patients with a delay longer than the median time had a 40% lower risk of dying compared with the patients with a shorter delay (hazard ratio=0.60; 95% CI 0.39-0.91; $p=0.02$). Even when studying a specific type of lung cancer, Myrdal et al. (24) observed a survival advantage for those patients with longer delays who were diagnosed with non-small cell lung cancer. They studied 466 patients diagnosed with non-small cell lung cancer and measured two types of delay, symptom to treatment delay and hospital delay. They found that patients with symptom to treatment delays of

less than 3 months had a 3-year survival of 11%, while patients with a delay of more than 6 months had a survival of 35%. They also found similar results when analyzing the relationship between hospital delay and survival. Patients with the shortest hospital delay (less than one month) had a 3-year survival of 19% compared to 43% for those patients with a hospital delay of more than 3 months. These results indicate that longer delay times are not associated with a poor prognosis. On the contrary, the prognosis was poorer in patients with a shorter delay.

The findings of our study revealed an inverse relationship between increased specialty delay and risk of all-cause mortality; however, the authors recognize the limitations of this study. As mentioned above, there was an inadequate sample size for the muscle-invasive disease groups, especially for stage T3 and T4, which had three patients each. In addition, some of the patients with muscle-invasive disease never received curative treatment with radical cystectomy due to comorbidities or the patient's refusal of treatment. Of the 40 patients who had muscle-invasive disease (stage T2-T4), only 17 patients (42.5%) were treated with radical cystectomy (data not shown). This finding is consistent with a Swedish study by Holmang et al. (25), who found that only 40% of patients with muscle-invasive bladder cancer were considered fit for radical cystectomy. Since this was a retrospective study reviewing the medical records of the study subjects, there was inadequate data collection on the cause of death and date of first symptoms. Thus, only overall mortality was calculated and disease-specific mortality was omitted from the analysis. In addition, complete

data on the dates of symptom onset would have made calculation of patient's delay (time interval from onset of symptoms to first medical consultation) possible. Without the data on patient's delay, an accurate description of the diagnostic delay (time interval from onset of symptoms to the establishment of a diagnosis) cannot be made. Instead, this study only used the specialty delay in the analysis, without taking into account the amount of time the patients have been symptomatic, which could contribute to the patient's outcome. Another limitation of this study is the omission of a multivariate analysis, which could have investigated factors such as age and comorbidity conditions that can affect survival from cancer. It is possible that the patients with shorter specialty delays had more comorbidities that may have subsequently determined the outcome, and not bladder cancer.

In general, there is a natural assumption that the sooner physicians can diagnose a cancer, the greater will be the chance of discovering it before it progresses and becomes incurable. However, this study did not confirm this assumption. In this study, there was a paradoxical finding that patients diagnosed more than 100 days after referral had a significant improvement in prognosis. In a society that is becoming increasingly litigious, one cannot rule out the possibility of a litigation based on a delayed diagnosis of cancer. Although this study observed a median specialty delay that is considerably longer than observed in other studies, the data demonstrates, within reasonable limits, that a patient in this healthcare system can be reassured that a delayed diagnosis is appears not to alter their prognosis. Even though our results

indicate that a longer delay before diagnosis of bladder cancer is not associated with a poorer prognosis, a timely diagnosis is still in the best interest of the patient's mental well-being. Requiring patients to wait longer for their diagnosis can cause additional psychological stress. Providing an early diagnosis can eliminate the guilt felt by patients for prolonging the patient delay interval and eliminate the blaming of the healthcare services for a long hospital delay.

In conclusion, our study observed a significant reduction in all-cause mortality for those patients diagnosed more than 100 days from consultation to the genitourinary service. In this setting, the triage effect may play an important role in the results observed in this study. However, to study this relationship without the triage effect would require a healthcare system with an excess of hospital resources or determination by a prospective study, which would be unethical to knowingly delay a patient's diagnosis of bladder cancer. These paradoxical findings confirm that the relationship between diagnostic delay and mortality is complex, and requires further investigation.

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